Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The aim was to estimate the cost-effectiveness of denosumab compared with various oral treatments for osteoporosis in postmenopausal women. The authors concluded that denosumab was a cost-effective alternative to oral osteoporosis treatments, particularly for patients at high risk of fracture, who were not expected to fully adhere to oral treatment. On the whole, the methods and results were sufficiently reported and appear to have been comprehensive. The conclusions reached by the authors appear to be appropriate.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The aim was to estimate the cost-effectiveness of denosumab, compared with various treatments for osteoporosis in postmenopausal women, using a model that included treatment adherence.

Interventions
Denosumab (60mg injected subcutaneously every six months) was compared with the oral bisphosphonates: generic alendronate, branded risedronate, and strontium ranelate, as well as no treatment for women with osteoporosis. The World Health Organization's definition of osteoporosis was used and this was a bone mineral density T-score at the femoral neck of -2.5 standard deviations or less.

Location/setting
Sweden/out-patient secondary care.

Methods
Analytical approach:
A Markov cohort model, with a six-month cycle length, was used. Treatment was assumed to last for five years. Each cycle included the probabilities of sustaining a fracture (wrist, hip, vertebral, or other osteoporotic), remaining healthy, or dying. The cohort entered the model at age 71 years (the mean age of women starting osteoporosis treatment, based on Swedish prescription data) and left at death or when they reached the age of 100 years (lifetime). A published Swedish model was used for adherence (Strom, et al. 2009, see ‘Other Publications of Related Interest’ below for bibliographic details). The authors stated that a societal perspective was taken.

Effectiveness data:
The main effectiveness estimates, which were the relative risks of fracture (hip, vertebral, wrist, and other), for the active comparators were from a published meta-analysis. Those for denosumab were from the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) randomised double-blind trial. The contribution from prior vertebral fractures to the fracture risk was assumed by the authors. The adherence estimates, defined as the medication possession ratio (MPR), for comparator treatments were from a large retrospective study of Swedish prescription data. Those for denosumab were from the Denosumab Adherence Preference Satisfaction (DAPS) study and were adjusted for the time-specific drop-out incidence in the Swedish prescription data. The offset time, which was the time over which the fracture risk linearly returned to the risk of an untreated population after treatment ended, was equal to the time on treatment and it was assumed to be the same for all treatments. Adverse events were considered in the sensitivity analysis. Treatment dropouts were assumed to occur during the first three years and persist for the treatment duration. The same estimates were used for all treatments.
Monetary benefit and utility valuations:
The utilities, for patients with fractures and the general population, were from published Swedish studies that used the European Quality of life (EQ-5D) questionnaire.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the main measure of benefit. Life-years were reported. Both were discounted at an annual rate of 3%.

Cost data:
The direct medical costs included bone mineral density measurement, physician and nurse visits, nursing home care, drugs, fracture treatment (hospital out-patient and in-patient), and proton-pump inhibitors for gastrointestinal events. The cost estimates were from a selection of Swedish sources, most of which were published. The costs were discounted at an annual rate of 3% and were in 2008 Euros (EUR). The most recent drug costs were used. Where necessary, the costs were converted from Swedish kronor to EUR and inflated using the Organisation for Economic Co-operation and Development (OECD) consumer price index statistics. The differences in consumption and production, or the costs in added life-years (CIALY) from increased health care for the elderly, were assessed.

Analysis of uncertainty:
One-way sensitivity and scenario analyses were performed on a large number of model parameters. The incremental results were presented in tables and graphs.

Results
Denosumab had an additional total cost of EUR 1,042 compared with no treatment, EUR 1,155 compared with alendronate, EUR 565 compared with risedronate, and EUR 258 compared with strontium ranelate. The QALYs gained with denosumab were 0.0721 compared with no treatment, 0.0426 compared with alendronate, 0.0490 compared with risedronate, and 0.0514 compared with strontium ranelate.

The cost per QALY gained (including the CIALY) for denosumab was EUR 14,458 compared with no treatment, EUR 27,090 compared with alendronate, EUR 11,545 compared with risedronate, and EUR 5,015 compared with strontium ranelate.

In general, when the discontinuation rate for denosumab decreased, the cost per QALY gained for all comparisons became closer to that for denosumab compared with no treatment. The cost-effectiveness improved with decreasing T-score for all comparisons. For patients with prior fracture, the cost per QALY gained was lower than for patients without prior fracture, and denosumab was cost saving compared with no treatment at a T-score of about -3.7 standard deviations or lower.

Using the persistence improvement data from the DAPS study for one year, the cost per QALY gained for denosumab versus alendronate was much worse, whilst the impact was less for the other comparators. Changes in the offset time after treatment ended had a significant impact on the results, but did not change the relationship between treatments. In all cases, the cost per QALY gained was below the commonly used thresholds of EUR 50,000 to 60,000 per QALY gained.

Authors' conclusions
The authors concluded that denosumab was a cost-effective alternative to oral osteoporosis treatments, particularly for patients at high-risk of fracture, who were not expected to adhere well to oral treatment.

CRD commentary
Interventions:
The authors selected active interventions that appear to have been appropriate and they included no treatment, which was relevant for patients who did not adhere to oral therapy. Some details were missing, such as the doses and frequency of the oral treatments.

Effectiveness/benefits:
The key effectiveness data for the active comparators were from a published meta-analysis of randomised placebo-
controlled trials, which should have provided high-quality data. The key data for denosumab were from one large randomised placebo-controlled trial. It was unclear whether a systematic review was undertaken to identify this evidence, and it is uncertain if the best available evidence was used. No data sources for the offset time assumptions were given, but the authors stated that, for the base case, they assumed a more realistic estimate than those assumed in previous models and they varied this parameter in the sensitivity analyses. QALYs were an appropriate benefit measure, given the impact of the disease on quality of life and survival. The methods used to derive the utility estimates were reported and these data were country specific. Future benefits were appropriately discounted.

Costs:
The direct medical and non-medical costs were included and appear to have reflected the perspective, but the details of the types of resources and how these were valued were not given for some cost categories. In particular, the fracture-related treatment costs and the CIA by L were not described. The CIA by L used in this study might not be relevant to other settings. It was not clear if the costs were adjusted for treatment withdrawals and compliance. The presentation of the costs as total categories restricts the replication of the results for other settings, but the cost estimates were fully referenced. The price year, time horizon, discount rate, inflationary adjustments, and currency were all reported.

Analysis and results:
The Markov model used to synthesise the evidence was described, with a diagram, and the results were reported clearly. The impact of uncertainty was investigated in a broad range of one-way sensitivity and scenario analyses, but the reasons for choosing the ranges were not provided. Probabilistic sensitivity analysis was not performed, and this could have assessed the overall uncertainty in the model. The reporting of the results was adequate, but only the incremental results were presented. The authors discussed the main limitations of their analysis.

Concluding remarks:
On the whole, the methods and results were sufficiently reported and appear to have been fairly comprehensive. The conclusions reached by the authors appear to be appropriate.

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